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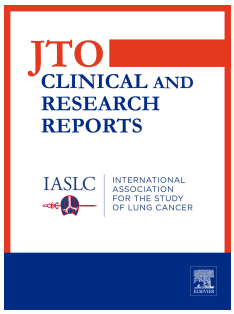


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# Impact of the COVID-19 Pandemic on Global Lung Cancer Clinical Trials: Why it matters to people with lung cancer

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The last decade of lung cancer research has seen rapid advances in early detection and treatment, and many new FDA-approved therapies for lung cancer. This has largely been possible due to clinical trials. Therapeutic, interventional clinical trials have become a critical component of lung cancer care. The National Comprehensive Cancer Network, the American Society of Clinical Oncology, and the European Society for Medical Oncology guidelines support clinical trial enrollment as standard of care for people with advanced-stage non-small cell lung cancer and extensive-stage small cell lung cancer in first- and subsequent-line settings. As of September 2021, worldwide there are approximately 1,500 actively recruiting interventional lung cancer trials that would require 405,786 participants.[1] Given that an estimated 2.2 million people were diagnosed with lung cancer globally in 2020,[2] these recruitment goals may seem attainable. However, due to various barriers, only 2%-8% of people with cancer participate in clinical trials.[3] This issue has only been exacerbated by the COVID-19 pandemic.

Declared a global pandemic in March 2020, COVID-19 has severely disrupted clinical trial conduct. The International Association for the Study of Lung Cancer (IASLC) commissioned a study to understand the impact of the pandemic on global early detection and therapeutics lung cancer trials, and mitigation steps taken by trial sites and sponsors to overcome the impact of the pandemic.[4] The study reported a 14% decline in patient enrollment between 2019 (pre-pandemic) and 2020 (post-pandemic). Disruptions were more notable in Phase 1 trials, which have numerous monitoring procedures, and those trials which involve infusion of investigational agents requiring frequent travel to study sites. Study sites reported fewer eligible participants, more deviation from protocol compliance, and increased trial suspensions. Regionally, Latin American sites took longer to recover from low recruitment than North American and Western European sites, suggesting the impact was amplified in regions that already have fewer trials available.

Participants' top concerns included fear of COVID-19 infection, travel restrictions to trial sites, and securing transportation. This led to logistical challenges such as impaired ability to travel to clinical trial sites.

The most effective mitigation strategies reported by sites included flexibility on location requirements (e.g., remote monitoring/diagnostics or using telehealth visits) or timing of procedures (e.g., spacing out visits or assessments) (Figure 1). While some of these strategies may reduce the burden of trial participation, others may lead to more participant anxiety and increase the impact of disparities among patients in terms of, for example, internet access, device access or comfort with technology, further impacting trial enrollment.

This study provides an excellent framework to reimagine **therapeutic, interventional** clinical trial design beyond the pandemic. Approaches should not compromise scientific rigor of trials, but should be patient centric, equitable, and minimize burden of participation. As a team of thoracic oncology leaders and international patient advocates, we provide recommendations (Table 1) for clinical trial stakeholders to consider as the lung cancer community prepares for the post-pandemic era.

**Role of clinical trial investigators and sponsors**: Clinical trial complexity has increased over the past decade, with trials requiring 59% more trial-related procedures from 2011 to 2015 compared to those from 2001 to 2005.[5] Almost half of sites surveyed in IASLC's study reported a desire to continue utilizing telehealth, remote monitoring (such as the use of routine blood and urine panels), and electronic consent processes. This focus on increased flexibility will allow more people to participate. Indeed, research suggests that structural barriers, such as travel burden, play an outsized role in low trial participation rates relative to other barriers, such as people not being offered trials or refusing participation.[6] Flexibility in access to trials can help those who are motivated to join but are deterred due to burdensome logistics. We encourage investigators and sponsors to develop standardized protocols for **remote monitoring** (allowing clinical, laboratory, and radiology examinations to be performed close to a participant's home, with easy assessment by the central trial site), **telehealth visits** (providing training to trial staff on the use of telehealth for remote procedures, and developing and using validated ePRO measures for symptom monitoring), **electronic consent procedures** (training staff, including patient advocates in developing e-consent procedures), **providing flexible options** (such as video or telephone conferencing), and **remote infusions** (when risk is deemed to be low, adverse event monitoring is conducted in real-time, and delivery, storage, and recording usage of experimental drug is streamlined) as mechanisms to foster enrollment and participation.[7, 8] It is important to note that digital technologies such as telehealth come with challenges in reimbursement, medical protection, and legal issues with regard to practice of medicine across state or equivalent boundaries. Until there is clarity on how these challenges will be resolved, continued implementation of telehealth will not be possible in the post-pandemic era. Digital technologies can facilitate participation for those who need to travel long distances to study sites. However, they need to be implemented in a manner that permits scalability, national and international applicability; and which does not introduce additional inequities in access for patients..

Another important consideration is the incorporation of optional COVID-19 vaccination as part of trial design.[9] Such designs will help people understand that they can choose to be vaccinated and participate in a clinical trial at the same time.

**Role of non-pharmaceutical funders**: Lung cancer research is funded by many different private and public sources, varying by country, and the impact of the pandemic on lung cancer research is still being evaluated. The role of non-pharmaceutical funders in drug development was underscored in a recent study that demonstrated that a substantial fraction of spending by the National Institutes of Health (NIH), the largest government funding agency in the United States, is contributing directly or indirectly to new therapies for all diseases, including lung cancer. [10] Governments and industry have focused pandemic-era funding on diagnostics, vaccines, and treatments for COVID-19, leaving research charities and not-for-profit organizations uncertain of future funding. Half of the Global Lung Cancer Coalition's (GLCC) members have seen income decreases since the start of the pandemic.[11] Large cancer research funders, such as the American Cancer Society, Canadian Cancer Society and Cancer Research UK, have seen large income reductions, leading to reduced research funding.[12] Lung cancer has traditionally been underfunded as a disease, with the NIH allocating only 6% of their overall

cancer research funding to lung cancer. We urge government funding agencies and private philanthropies to continue to invest in life-saving research that will fuel the drug development pipeline. Lung cancer now leads the solid tumor oncology space with the highest number of treatment options in clinical trials. A decrease in funding will impede progress against this disease.

**Role of regulatory agencies**: During the early stages of the pandemic, regulatory agencies, such as the United States Food and Drug Administration (USA), the European Medicines Agency, Health Products Regulatory Authority (Ireland), and the Healthcare Products Regulatory Agency (United Kingdom), rapidly issued guidance on clinical trial conduct. Common themes with **direct** participant impact revolved around allowing remote monitoring of certain trials through local labs, the impact of COVID-19 status on trial eligibility and participation, mail-order medication delivery, and use of electronic consent procedures. As advocates, we applaud regulators for reacting to the pandemic to ensure that clinical trials continue. It is currently unclear how regulators see these strategies being incorporated into clinical trial design beyond the pandemic. We hope that positive changes made during the pandemic will remain in post-pandemic times, given that these changes reduced existing (pre-COVID-19) barriers. Clinical investigators and sponsors will be open to adopting flexible trial designs only if regulators and health technology assessments (HTAs) do not see these designs as impeding registration, drug approval, and reimbursement. Another worry is that changes or a temporary halt to existing trials early in the pandemic will affect the quality or interpretability of trial data and therefore influence future licensing decisions. We encourage regulators to weigh current modifications and issue guidance on how they propose to proceed with regulatory decisions, especially for pivotal clinical trials that are still ongoing. Lastly, we request regulators to provide clear guidance on how history or current exposure to SARS-CoV-2 will affect eligibility, trial design, and drug approval and labeling.

The COVID-19 pandemic presented an unprecedented global health challenge, the effects of which will continue to be felt for years to come. It also demonstrated how the global scientific community rapidly pivoted and partnered to develop life-saving vaccines that become available in a time frame that most felt was unattainable. The lung cancer community also rapidly mobilized and formed international consortiums such as the COVID-19 and Lung Cancer Consortium (CLCC) and TERAVOLT, to understand the impact of the pandemic on the care of patients. This momentum bears testimony to the power of science and collaboration.

Government agencies (such as the National Cancer Institute in the United States) and professional organizations (such as the American Society of Clinical Oncology and the European Society for Medical Oncology) have issued guidance on clinical trial conduct during the pandemic.[7, 8, 13] The purpose of this commentary is to provide the patient advocacy perspective to these recommendations. We acknowledge that incorporating recommendations provided in the framework in this commentary is complex and contingent on several site-specific, policy-specific, and country-specific factors. As advocates, we remain optimistic that the lung cancer clinical trial ecosystem will continue to learn, partner, and innovate – to ensure

that clinical trial designs become more patient-centric, and more people continue to have access to life-saving therapies through these trials.

**References:**


1. ClinicalTrials.gov. Actively recruiting interventional trials in lung cancer, as of September 19, 2021. 2021 Available at www.clinicaltrials.gov.
2. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* 2021;71:209-249.
3. Unger JM, Hershman DL, Till C, et al. "When Offered to Participate": A Systematic Review and Meta-Analysis of Patient Agreement to Participate in Cancer Clinical Trials. *J Natl Cancer Inst* 2021;113:244-257.
4. Smeltzer M. PL02.09 - International Association for the Study of Lung Cancer (IASLC) Study of the Impacts of COVID-19 on International Lung Cancer Clinical Trials. *World Conference on Lung Cancer 2021*. Denver: International Association for the Study of Lung Cancer; 2021.
5. Getz KA, Campo RA. New Benchmarks Characterizing Growth in Protocol Design Complexity. *Ther Innov Regul Sci* 2018;52:22-28.
6. Unger JM, Vaidya R, Hershman DL, et al. Systematic Review and Meta-Analysis of the Magnitude of Structural, Clinical, and Physician and Patient Barriers to Cancer Clinical Trial Participation. *J Natl Cancer Inst* 2019;111:245-255.
7. Castelo-Branco L, Awada A, Pentheroudakis G, et al. Beyond the lessons learned from the COVID-19 pandemic: opportunities to optimize clinical trial implementation in oncology. *ESMO Open* 2021;6:100237.
8. Flaherty KT, Doroshow JH, Galbraith S, et al. Rethinking Cancer Clinical Trial Conduct Induced by COVID-19: An Academic Center, Industry, Government, and Regulatory Agency Perspective. *Cancer Discov* 2021;11:1881-1885.
9. Desai A, Gainor JF, Hegde A, et al. COVID-19 vaccine guidance for patients with cancer participating in oncology clinical trials. *Nat Rev Clin Oncol* 2021;18:313-319.
10. Galkina Cleary E, Beierlein JM, Khanuja NS, et al. Contribution of NIH funding to new drug approvals 2010-2016. *Proc Natl Acad Sci U S A* 2018;115:2329-2334.
11. GLCC. Impact of COVID-19: findings from a GLCC members survey. Available at https://www.lungcancercoalition.org/2020/06/19/impact-of-covid-19-findings-from-a-glcc-members-survey/. Accessed September 21 2021.
12. Burki TK. Cuts in cancer research funding due to COVID-19. *Lancet Oncol* 2021;22:e6.
13. Doherty GJ, Goksu M, de Paula BHR. Rethinking cancer clinical trials for COVID-19 and beyond. *Nat Cancer* 2020:1-5.

**Figure 1**: Impact of COVID-19 trial modifications on patient burden of trial participations. Numbers in parenthesis indicate the percentages of sites reporting the use of a specific modification.

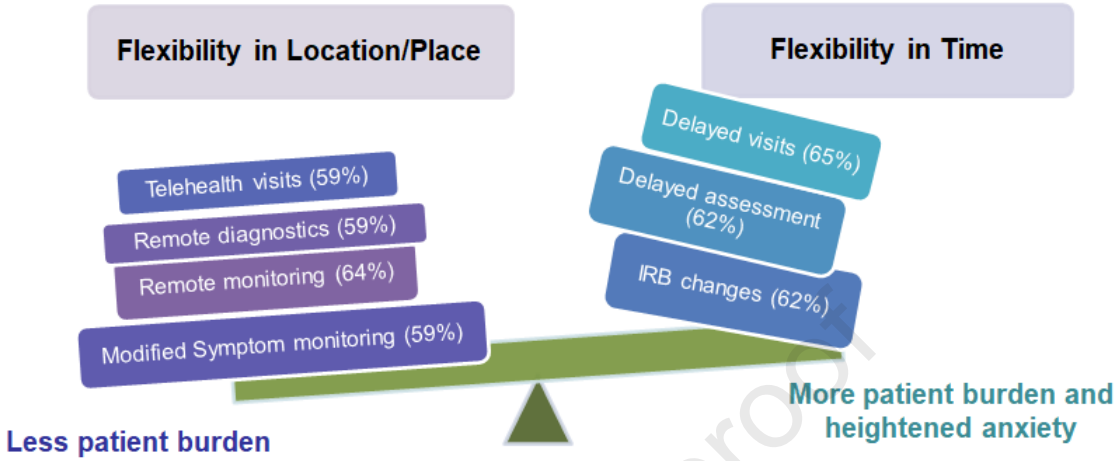


**Table 1**: Patient-centric recommendations for conduct of clinical trials for thoracic oncology stakeholders

| Stakeholder | Recommendations |
|---|---|
| Clinical trial investigators and sponsors | • Conduct remote clinical, laboratory, and radiological assessment of on-trial patients as applicable to the Phase of the trial<br>• Allow for remote infusions (when risk is deemed to be low; distribution, storage, and recording usage of the study drug is possible at local infusion centers; and adverse event monitoring is carried out real-time) or mail-order targeted therapy delivery<br>• Develop, train staff, and implement digital protocols for:<br>  ○ Patient recruitment, engagement, and retention in clinical trials<br>  ○ ePROs for remote symptom monitoring<br>  ○ Telehealth visits that incorporate video or telephone conferencing – based on individual patient preferences |
| Regulatory agencies | • Provide recommendations on how registrational trials provisionally halted during the pandemic should proceed so that registration is not hampered<br>• Allow flexibility in patient-centric pandemic regulations (for example, electronic consent, mail-order medication, |

| | |
|---|---|
| | and remote monitoring) to proceed in the post-COVID-19 era<br>• Provide guidance on how history or current exposure to SARS-CoV-2 will affect eligibility, trial design, and drug approval and labeling |